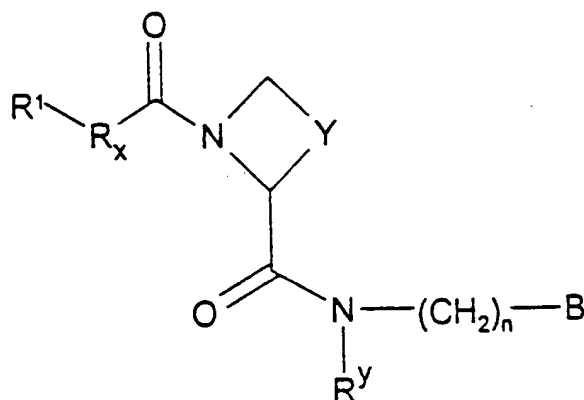


AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1 (currently amended). A compound of formula I,



wherein

R¹ represents H, C₁₋₄ alkyl (optionally substituted by one or more substituents selected from cyano, halo, OH, C(O)OR^{1a} or C(O)N(R^{1b})R^{1c}) or OR^{1d};

R^{1d} represents H, C(O)R¹¹, SiR¹²R¹³R¹⁴ or C₁₋₆ alkyl, which latter group is optionally substituted or terminated by one or more substituent selected from OR¹⁵ or (CH₂)_qR¹⁶;

R¹², R¹³ and R¹⁴ independently represent H, phenyl or C₁₋₆ alkyl;

R¹⁶ represents C₁₋₄ alkyl, phenyl, OH, C(O)OR¹⁷ or C(O)N(H)R¹⁸;

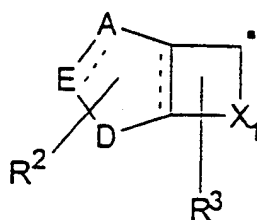
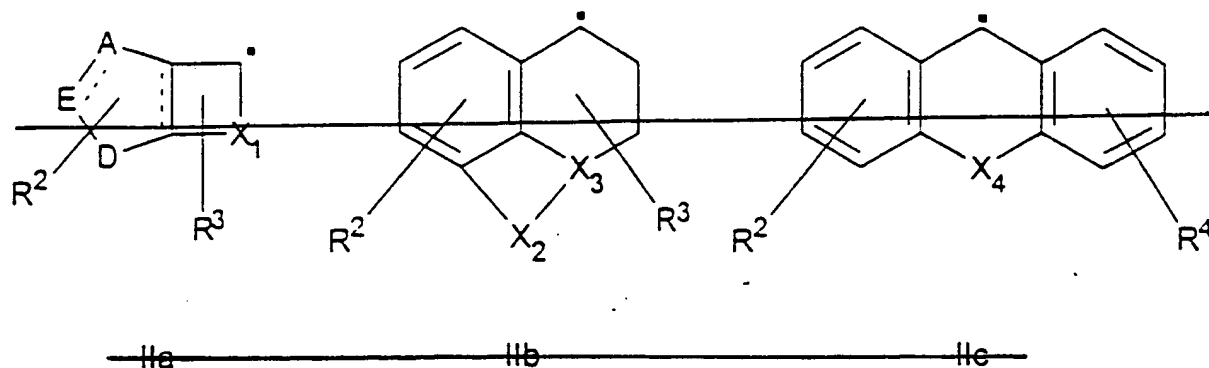
R¹⁸ represents H, C₁₋₄ alkyl or CH₂C(O)OR¹⁹;

R¹⁵ and R¹⁷ independently represent H, C₁₋₆ alkyl or C₁₋₃ alkylphenyl;

R^{1a}, R^{1b}, R^{1c}, R¹¹ and R¹⁹ independently represent H or C₁₋₄ alkyl; and

q represents 0, 1 or 2;

R_x represents a structural fragment of formula IIa, IIb or IIc,



IIa

wherein

the dotted lines independently represent optional bonds;

A and E independently represent O or S, CH or CH₂ (as appropriate), or N or N(R²¹) (as appropriate);

D represents -CH₂-, O, S, N(R²²), -(CH₂)₂-, -CH=CH-, -CH₂N(R²²)-,
 -N(R²²)CH₂-, -CH=N-, -N=CH-, -CH₂O-, -OCH₂-, -CH₂S- or -SCH₂-;

X_1 represents C_{2-4} alkylene; ~~C_{2-3} alkylene interrupted by Z ; $-C(O)-Z-A^1-Z-A^3$;~~

~~$-Z-C(O)-A^1$; $-CH_2-C(O)-A^1$; $-Z-C(O)-Z-A^2$; $-CH_2-Z-C(O)-A^2$;~~

~~$-Z-CH_2-C(O)-A^2$; $-Z-CH_2-S(O)_m-A^2$; $-C(O)-A^3$; $-Z-A^3$; or $-A^3-Z$;~~

X_2 represents ~~C_{2-3} alkylene, $-C(O)-A^4$ or $-A^4-C(O)-$;~~

X_3 represents ~~CH or N~~;

X_4 represents a single bond, O, S, C(O), $N(R^{23})$, ~~$CH(R^{23})$;~~

~~$CH(R^{23})-CH(R^{24})$ or $-C(R^{23})-C(R^{24})$;~~

A^1 represents a single bond or C_{1-2} alkylene;

A^2 represents a single bond or $-CH_2-$;

A^3 represents C_{1-3} alkylene;

A^4 represents ~~$C(O)$ or C_{1-2} alkylene~~;

Z represents, at each occurrence, Θ , $S(O)_m$ or $N(R^{25})$;

R^2 and R^4 independently represent represents one or more optional substituents

selected from C_{1-4} alkyl, C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo substituent), methylenedioxy, halo, hydroxy, cyano, nitro, $S(O)_2NH_2$, $C(O)OR^{26}$, SR^{26} , $S(O)R^{26a}$, $S(O)_2R^{26a}$ or $N(R^{27})R^{28}$;

R^3 represents one or more optional substituents selected from OH, C_{1-4} alkoxy, C_{1-6} alkyl (optionally substituted by one or more halo group), or $N(R^{29a})R^{29b}$;

R^{25} , R^{29a} and R^{29b} independently represent H, C_{1-4} alkyl or $C(O)R^{30}$;

R^{26} represents H or C_{1-4} alkyl;

R^{26a} represents C_{1-4} alkyl;

R^{27} and R^{28} independently represent H, C_{1-4} alkyl or $C(O)R^{30}$, or together represent C_{3-6} alkylene, thus forming a 4- to 7-membered ring, which ring is optionally

substituted, on a carbon atom that is α to the nitrogen atom, with an =O group;

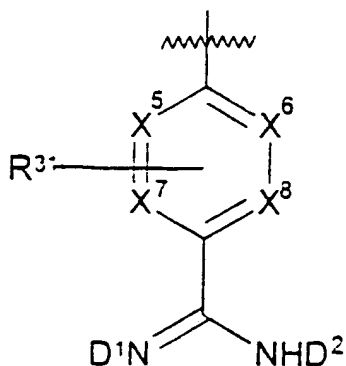
R^{21} , R^{22} , R^{23} , R^{24} and R^{30} independently represent, at each occurrence, H or C_{1-4} alkyl;

Y represents CH_2 , $(CH_2)_2$, $CH = CH$ (which latter group is optionally substituted by C_{1-4} alkyl), $(CH_2)_3$, $CH_2CH=CH$ or $CH=CHCH_2$ (which latter three groups are optionally substituted by C_{1-4} alkyl, methylene, =O or hydroxy);

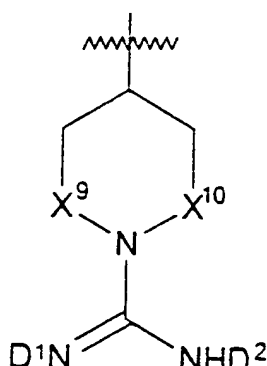
R^y represents H or C_{1-4} alkyl;

n represents 0, 1, 2, 3 or 4; and

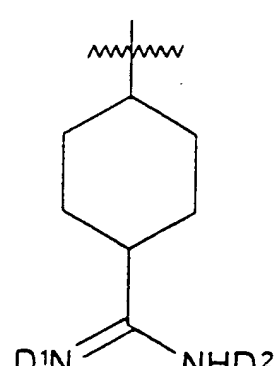
B represents a structural fragment of formula IIIa, IIIb or IIIc



IIIa



IIIb



IIIc

wherein

X^5 , X^6 , X^7 and X^8 independently represent CH, N or N-O;

X^9 and X^{10} independently represent a single bond or CH_2 ;

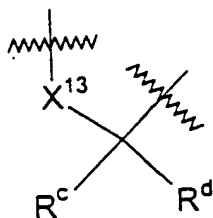
R^{31} represents an optional substituent selected from halo, C_{1-4} alkyl (which group is optionally substituted by one or more halo group), $N(R^{32})R^{33}$, OR^{34} or SR^{35} ;

R^{32} and R^{33} independently represent H, C_{1-4} alkyl or $C(O)R^{36}$;

R^{34} , R^{35} and R^{36} independently represent H or C_{1-4} alkyl; and

one of D^1 and D^2 represents H, and the other represents H, OR^a , NHR^a ,

$C(=X^{11})X^{12}R^b$, or D^1 and D^2 together represent a structural fragment of formula IVa:-



IVa

R^a represents H or $-A^5[X^{14}]_n[C(O)]_rR^e$;

R^b represents $-A^5[X^{14}]_n[C(O)]_rR^e$;

A^5 represents, at each occurrence, a single bond or C_{1-12} alkylene (which alkylene group is optionally interrupted by one or more O, $S(O)_m$ and/or $N(R^f)$ group, and is optionally substituted by one or more of halo, OH, $N(H)C(O)R^g$, $C(O)N(R^g)R^h$, C_{3-7} cycloalkyl (which cycloalkyl group is optionally interrupted by one or more O, $S(O)_m$ and/or $N(R^f)$ group and/or is optionally substituted by one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo, $=O$ or $=S$), Het and C_{6-10} aryl (which aryl and Het groups are themselves optionally substituted by one or more substituents selected from C_{1-6} alkyl (optionally substituted by one or more halo substituent), C_{1-6} alkoxy, halo, cyano, $C(O)OR^g$, $C(O)N(R^g)R^h$ and $N(R^f)R^g$);

R^c and R^d both represent H; or one of R^c and R^d represents H or C_{1-7} alkoxy and the other represents C_{1-17} alkyl (which alkyl group is optionally interrupted by one or more O atoms); or R^c and R^d together represent C_{3-8} cycloalkyl, which cycloalkyl group

is interrupted by one or more O, S(O)_m and/or N(R^f) group;

R^g represents, at each occurrence, H, C₁₋₁₂ alkyl (which alkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and/or is optionally substituted by one or more substituents selected from halo, OH, N(H)C(O)R^g and C(O)N(R^g)R^h), A⁷-C₃₋₇-cycloalkyl (which cycloalkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group and/or is substituted by one or more substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, =O and =S), A⁷-C₆₋₁₀ aryl or A⁷-Het (which aryl and Het groups are optionally substituted by one or more substituents selected from C₁₋₆ alkyl (optionally substituted by one or more halo substituent), C₁₋₆ alkoxy, halo, cyano, C(O)OR^g, C(O)N(R^g)R^h and N(R^f)R^g);

A⁷ represents a single bond or C₁₋₇ alkylene (which alkylene group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and/or are optionally substituted by one or more of halo, OH, N(H)COR^g and CON(R^g)R^h);

Het represents, at each occurrence, a five- to ten-membered heteroaryl group, which may be aromatic in character, containing one or more nitrogen, oxygen or sulphur atoms in the ring system;

n and r independently represent 0 or 1;

X¹¹, X¹² and X¹⁴ independently represent O or S;

X¹³ represents O or N(R^f);

R^f represents, at each occurrence, H, C₁₋₄ alkyl or C(O)R^g;

R^g and R^h independently represent, at each occurrence, H or C₁₋₄ alkyl; and

m represents, at each occurrence, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof;

provided that:

- ~~(a) A and E do not both represent O or S;~~
- ~~(b) E and D do not both represent O or S;~~
- ~~(c) when R^1 represents OR^{1d} and X_1 represents $C(O)-Z-A^1$,
 $-Z-CH_2S(O)_m-A^2$ or $-Z-C(O)-Z-A^2$, then A^1 or A^2 (as appropriate) do not represent~~
a single bond;
- ~~(f) when X_4 represents $CH(R^{23})$, R^1 does not represent OH;~~
- ~~(g) (a) when A^5 represents a single bond, then n and r both represent 0;~~
- ~~(f) (b) when A^5 represents C_{1-12} alkylene, then n represents 1;~~
- ~~(g) (c) when A^5 represents $-CH_2-$, n is 1 and r is 0, then R^e does not represent H;~~

and

~~(h) (d) the compound is not:-~~

- (S)- or (R)-1 -hydroxy-7-methoxytetralin-1-yl-C(O)-Pro-Pab;
- (R)- or (S)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Pro-Pab;
- (S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
- (R)- or (S)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab;
- 1-hydroxy-5-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
- 1-hydroxy-5,7-dimethyltetralin-1-yl-C(O)-Aze-Pab x HOAc;
- 1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab x HOAc;
- 1-hydroxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
- 7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
- (R)- or (S)-7-methoxy-1-methyltetralin-1-yl-C(O)-Aze-Pab;
- 4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab x OAc;

(*S*)- or (*R*)-1-hydroxy-4-methoxyindan-1-yl-C(O)-Aze-Pab;
1-hydroxy-5-methoxytetralin-1-yl-C(O)-Aze-Pab(OH);
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(OH);
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab(OH);
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab(OMe);
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
(C(O)OCH₂CCl₃);
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
(C(O)OCH₂CH₃);
7-methoxy-1-allyltetralin-1-yl-C(O)-Aze-Pab x HOAc;
(*S*)- or (*R*)-1-hydroxy-7-chlorotetralin-1-yl-C(O)-Pro-Pab;
1-*n*-propyl-7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
6-chloro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6,8-dichloro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6-fluoro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
4-hydroxy-6-methylchroman-4-yl-C(O)-Aze-Pab x HOAc;
8-chloro-4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6-chloro-4-hydroxy-8-methylchroman-4-yl-C(O)-Aze-Pab x HOAc;
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-*i*-Pr);
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Et);
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Ch);
(*S*)- or (*R*)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-allyl);

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Bzl);

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-

(CO-O-methallyl);

1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab(OH);

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Val);

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-(Me)Pab; or

9-hydroxyfluoren-9-yl-C(O)-Aze-Pab x HOAc.

2 (original). A compound as claimed in Claim 1 wherein R¹ represents OH or C₁₋₄ alkyl (which latter group is optionally substituted by cyano or OH).

3 (canceled).

4 (currently amended). A compound as claimed in claim 1 wherein, when R_x represents a the dotted lines in the structural fragment of formula IIa, ~~then the dotted lines represent bonds, A and E both represent CH and D represents -CH=CH-~~

5 (currently amended). A compound as claimed in claim 1 wherein, when R_x represents a structural fragment of formula IIa, ~~X₁ represents optionally unsaturated C₂- or C₃-alkylene, or -Z-A³ (in which Z represents O, S(O)_m or N(R²⁵) (in which R²⁵ is as defined above or represents C₁₋₄ alkyl or C(O)R³⁰ and m and R³⁰ are as defined above) and A³ represents C₁- or C₂-alkylene (which latter group is optionally unsaturated))~~

6 (previously presented). A compound as claimed in claim 1 wherein Y represents CH_2 , $(\text{CH}_2)_2$ or $(\text{CH}_2)_3$.

7 (previously presented). A compound as claimed in claim 1 wherein B represents a structural fragment of formula IIIa in which X^5 , X^6 , X^7 and X^8 all represent CH.

8 (previously presented). A compound as claimed in claim 1 wherein, when D^1 and D^2 together represent a structural fragment of formula IVa, in which X^{13} is O, then one of R^c and R^d represents H or C_{1-7} alkoxy and the other represents C_{1-7} alkyl.

9 (previously presented). A compound as claimed in claim 1, wherein, when D^1 or D^2 represents OR^a and R^a represents $-\text{A}^5[\text{X}^{14}]_n[\text{C}(\text{O})]_r\text{R}^e$, and

(i) A^5 is a single bond, then R^e is:-

(1) A^7 -aryl, optionally substituted by one or more halo, C_{1-6} alkoxy, C_{1-6} alkyl or halo- C_{1-6} -alkyl substituents; or

(2) H or linear, branched, optionally unsaturated, and/or cyclic, C_{1-12} alkyl, which cyclic alkyl group is optionally interrupted by an O atom and, optionally, a further O atom or $\text{S}(\text{O})_m$ group; or when

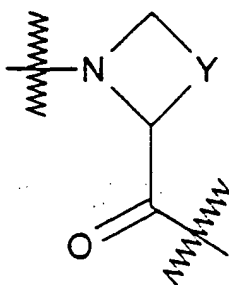
(ii) A^5 is linear or branched C_{1-12} alkylene, X^{14} is O and r is 0, then R^e is C_{1-3} alkyl or A^7 -aryl, in which A^7 is a single bond.

10 (previously presented). A compound as claimed in claim 1, wherein, when D^1

or D² represents OR^a, then R^a is H or C₁₋₄ alkyl.

11 (previously presented). A compound as claimed in claim 1, wherein, when D¹ or D² represents -C(=X¹¹)X¹²R^b, in which X¹¹ represents O and X¹² represents O or S, and, in which R^b group, A⁵ represents a single bond then R^e represents optionally unsaturated C₁₋₆ alkyl, A⁷-C₆₋₁₀-aryl (in which A⁷ represents a single bond or C₁₋₂ alkylene, and which A⁷-C₆₋₁₀-aryl group is optionally substituted by one or more halo, C₁₋₄ alkyl and/or C₁₋₄ alkoxy groups), or A⁷-C₃₋₇-cycloalkyl, in which A⁷ represents a single bond or linear or branched C₁₋₇ alkylene, and which cycloalkyl group is optionally substituted by C₁₋₃ alkyl.

12 (previously presented). A compound of formula I, as defined in claim 1, wherein the fragment



is in the S-configuration.

13 (previously presented). A pharmaceutical formulation including a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a

pharmaceutically acceptable adjuvant, diluent or carrier.

14-20 (canceled).

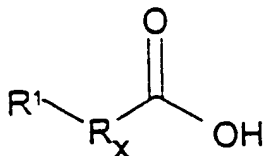
21 (previously presented). A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

22 (original). A method as claimed in Claim 21, wherein the condition is thrombosis.

23 (original). A method as claimed in Claim 21, wherein the condition is hypercoagulability in blood and tissues.

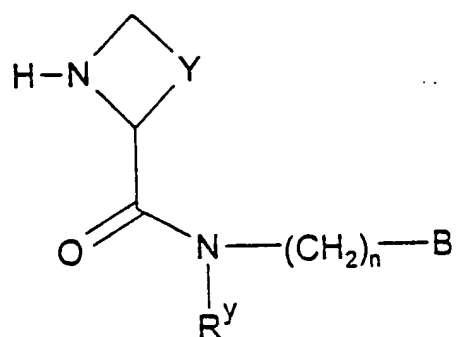
24 (original). A process for the preparation of compounds of formula I which comprises:

- (i) the coupling of a compound of formula IV,



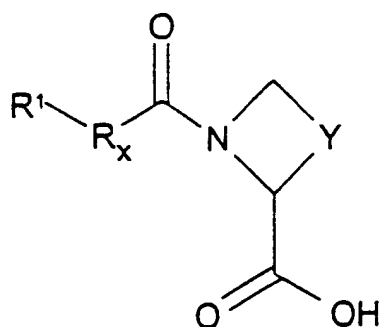
IV

wherein R¹ and R_x are as defined in Claim 1 with a compound of formula V,

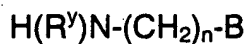


wherein R^y , Y, n and B are as defined in Claim 1;

(ii) the coupling of a compound of formula VI,



wherein R^1 , R_x and Y are as defined in Claim 1 with a compound of formula VII,

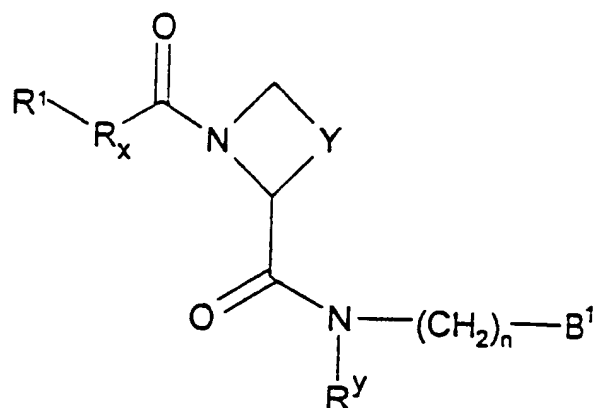


VII

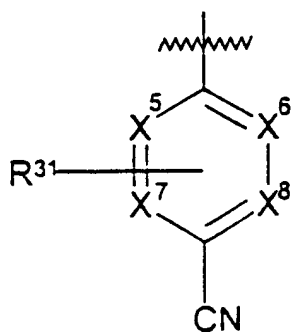
wherein R^y , n and B are as defined in Claim 1;

(iii) for compounds of formula I in which D^1 or D^2 represents OR^a or NHR^a ,

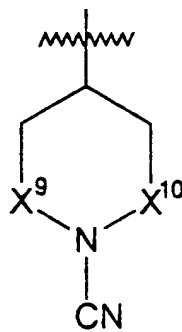
reaction of a compound of formula VIII,



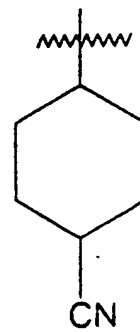
wherein B¹ represents a structural fragment of formula III d, III e or III f



III d



III e



III f

and R¹, R_x, Y, R^y, n, R³¹, X⁵, X⁶, X⁷, X⁸, X⁹ and X¹⁰ are as defined in Claim 1 with
 a compound of formula IX,



IX

wherein X^a represents O or NH and R^a is as defined in Claim 1;

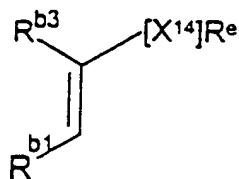
(iv) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a,
reaction of a compound of formula I in which D¹ or D² (as appropriate) represents
C(O)OR^{b1}, in which R^{b1} represents a protecting group with a compound of formula IX as
defined above;

(v) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, R^a represents -A⁵[X¹⁴]_n[C(O)]_rR^e, in which A⁵ does not represent a single bond, and n represent 1, reaction of a compound of formula I in which D¹ or D² (as appropriate) represents OH or NH₂, with a compound of formula X,



wherein L¹ represents a suitable leaving group, A^{5a} represents A⁵, as defined in Claim 1 except that it does not represent a single bond, and X¹⁴, r and R^e are as defined in Claim 1;

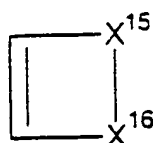
(vi) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, R^a represents -A⁵[X¹⁴]_n[C(O)]_rR⁹, in which A⁵ represents C₂₋₁₂ alkylene, which alkylene group is branched at the carbon atom that is α to the O or N atom of OR^a or NHR^a (as appropriate), and which group is optionally branched at the carbon atom that is β to that atom, n represents 1, r represents 0 and R⁹ is as defined in Claim 1, reaction of a compound of formula I in which D¹ or D² (as appropriate) represents OH or NH₂, with a compound of formula XI,



XIII

or a geometrical isomer thereof, or a mixture of such geometrical isomers, in which R^{b1} and R^{b3} each represent H or an alkyl group, provided that the total number of carbon atoms provided by R^{b1} and R^{b3} does not exceed 10, and wherein X^{14} and R^e are as defined in Claim 1;

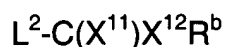
(vii) for compounds of formula I in which D^1 or D^2 represents OR^a or NHR^a , represents $-A^5[X^{24}]_n[C(O)]_rR^e$, in which A^5 represents a single bond, and R^e represents A^7 -C₃₋₆-cycloalkyl, in which A^7 represents a single bond, and the cycloalkyl group is interrupted by at least one O or S atom, which atom is between the carbon atom at the point of attachment to the O or NH group of OR^a or NHR^a , and a carbon atom that is α to that point of attachment, and which cycloalkyl group is optionally interrupted by one or more O or S(O)_m group and/or optionally substituted by one or more =O group, reaction of a compound of formula I, in which D^1 or D^2 (as appropriate) represents OH or NH₂, with a compound of formula XII,



XII

wherein X^{15} represents O or S and X^{16} represents C₁₋₄ alkylene (which alkylene group is optionally interrupted by one or more O or S(O)_m group and/or optionally substituted by one or more =O group);

(viii) for compounds of formula I in which D^1 or D^2 represents $C(X^{11})X^{12}R^b$, reaction of a compound of formula I in which D^1 and D^2 both represent H with a compound of formula XIII,



XIII

wherein L^2 represents a suitable leaving group, and X^{11} , X^{12} and R^b are as defined in Claim 1;

(ix) for compounds of formula I in which D^1 and D^2 together represent a structural fragment of formula IVa, reaction of a corresponding compound of formula I in which D^1 or D^2 represents OH or NHR^f (in which R^f is as defined in Claim 1), with a compound of formula XV,



XV

wherein R^{c1} and R^{c2} both represent $-OR^{c3}$, in which R^{c3} represents C_{1-3} alkyl, or together represent $=O$, and R^c and R^d are as defined in Claim 1;

(x) for compounds of formula I in which one or more of X^5 , X^6 , X^7 and X^8 represent N-O, oxidation of a corresponding compound of formula I in which X^5 , X^6 , X^7 and/or X^8 (as appropriate) represent(s) N; or

(xi) for compounds of formula I in which any one of Z , X_1 , R^2 , R^4 , A^5 , A^7 , R^c , R^d and/or R^e comprises or includes a (O) or a $S(O)_2$ group, oxidation of a corresponding compound of formula I (or a compound corresponding to a compound of formula I) wherein Z , X_1 , R^2 , R^4 , A^5 , A^7 , R^c , R^d and/or R^e (as appropriate) comprise(s) or include(s) a S group;

(xii) for compounds of formula I in which D^1 and D^2 both represent H, removal of a OR^a , NHR^a or $C(=X^{11})X^{12}R^b$ group (in which R^a , R^b , X^{11} and X^{12} are as defined in Claim 1), or removal of a structural fragment of formula IVa as defined in Claim 1, from a corresponding compound of formula I; or

(xiii) introduction and/or interconversion of a substituent on an aromatic and/or

non-aromatic, carbocyclic and/or heterocyclic ring in a corresponding compound of formula I.